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Platform presentations

DUPLICATION AND DELETION OF CHROMOSOME 17p11.2 IN DEMYELINATING NEUROPATHIES

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Hereditary motor and sensory neuropathy (HMSN) type I is commonly associated with a 1.5 Mb duplication of chromosome 17p11.2 which contains the peripheral myelin protein gene PMP-22. The duplication is flanked by repeat sequences and probably arises from unequal recombination; its reciprocal product, a deleted chromosome 17, has been shown to underlie hereditary liability to pressure palsies (HLPP).

DNA was analysed from patients with HMSN I, HLPP, other types of HMSN, possibly sporadic cases of HMSN I, and others with acquired demyelinating neuropathies (paraproteinaemic and chronic inflammatory; CIDP). Duplication of 17p11.2 was observed in members of 69 families with HMSN I. Sixty had affected relatives, seven did not, and two were adopted. Three patients had unusual phenotypes (bulbar palsy, an associated IgM kappa paraproteinaemic neuropathy, and the features of CIDP). In nine families without the duplication, there was no male to male transmission in four and they probably have the X-linked type of HMSN. Deletion of 17p11.2 was found in many patients with HLPP, and some in whom this diagnosis was not obvious. DNA analysis is useful in distinguishing different types of demyelinating neuropathy, and in genetic counselling.

AXONAL FORM OF GUILLAIN-BARRÉ SYNDROME: EVIDENCE FOR MACROPHAGE- ASSOCIATED DEMYELINATION

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The clinicopathological findings are reported in a patient with severe pure motor and axonal Guillain-Barré syndrome who died 29 days after onset. An electrophysiological study was performed on day 18. There was marked reduction of compound motor action potential amplitudes and presence of muscle denervation potentials. Motor and sensory conduction velocities of median nerve were normal. The peroneal nerve was inexcitable at ankle but its latency from knee to tibialis anterior was normal. F waves were absent or delayed. Together with conventional paraffin embedded material, our morphological study included semithin and ultrathin sections of L₅-S₁ ventral and dorsal roots and sural nerve, and morphometry and teased fibre preparation of L₅ ventral root was performed. The

major burden of pathological changes fell on the ventral spinal roots and consisted of widespread endoneurial lipid-laden macrophages, segmental de- and re-myelination, axonal degeneration, loss of myelinated fibres and clusters of small regenerating fibres. Rare perivascular lymphocytes were seen. These findings suggest that the pathological framework of pure motor and axonal Guillain-Barré syndrome is a massive ventral root macrophage-associated demyelination with secondary axonal degeneration.

NATIONAL MOTOR NEURON DISEASE TWIN STUDY: FINAL RESULTS

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Using a novel methodology, termed the death discordant twin method, the world's largest twin sample for motor neuron disease (MND) has been collected consisting of 75 pairs: 24 monozygotic and 51 dizygotic. This involved identifying all twins with death certificates classified under ICD rubric 335.2 (MND) between 1979 and 1989 inclusive. This allowed estimation of the genetic contribution in sporadic MND; and formation of matched pairs for a case-control study of environmental factors.

Four monozygotic probands from two concordant pairs were identified, producing a concordance rate of 17.4%. Two probands had to be removed from the calculations because they came from a pedigree with familial MND. This gave a correlation of liability for MND among monozygotic twins of 0.717 (SE 0.13). No dizygotic concordant pairs were found. The estimated coefficient of genetic determination for MND was 0.60 (range 0.38-0.85). This supports a multifactorial aetiology for MND—that is, a single gene defect is excluded.

Analysis of the case-control data produced elevated odds ratios (OR) with relatively wide 95% confidence intervals (CI), for "regular vehicle maintenance" (OR = 7.0 (CI 1.3-89.9)), and "occupational paint usage" (OR = 3.75 (CI 1.1-17.1)), which held true during conditional logistic regression modelling. All the other individual factors had weaker associations, but were related because they involved exposure to petroleum and solvent based chemicals.

ANTIBODIES AGAINST GANGLIOSIDES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND NEUROLOGICAL INVOLVEMENT

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The relationship between antibodies against several gangliosides and the neuropsychi-

atric manifestations of systemic lupus erythematosus (SLE) were investigated. The pathogenesis of neuropsychiatric abnormalities in SLE has not been clearly defined and the search for pathogenic mechanisms has focused on the importance of several autoantibodies. A strong relationship between antibodies against gangliosides and CNS-SLE has been reported.

Serum samples from 147 patients were studied. Included were 107 patients with SLE, 54 of whom had experienced neuropsychiatric manifestations, and 40 normal subjects. All serum samples were tested by enzyme linked immunosorbent assay (ELISA) for IgG and IgM reactivity with asialoGM1, GM1 and GD1a (Sigma).

Nineteen of 107 patients with SLE (17.7%) were positive for asialoGM1 (13 IgM, 4 IgG, 2 both isotypes), 28 out of 107 (26.1%) were positive for GM1 (13 IgM, 10 IgG, 5 both isotypes) and 33 out of 107 (30.8%) were positive for GD1a (21 IgM, 6 IgG, 6 both isotypes). Eleven of 54 patients with CNS-SLE (20.3%) had anti-asialoGM1 antibodies, 20 out of 54 (37.0%) had anti-GM1 antibodies and 23 out of 54 (42.5%) had anti-GD1a antibodies.

It is concluded that the incidence of anti-GM1 and anti-GD1a antibodies was significantly higher in SLE patients with neurologic symptoms than in those without. No correlation was found between antibodies against gangliosides and those directed against cardiolipin.

NEUROLOGICAL ADVERSE DRUG REACTIONS

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A retrospective study was carried out of 2574 outpatients (1431 women and 1143 men, mean age = 52.18 years), who presented to our neurological clinic. Adverse drug reactions (ADR) affecting the nervous system were studied. These were detected in 212 (8.24%) patients, more frequently in women than in men (65.57% v 34.43%; $p < 0.01$, χ^2). The mean age of those patients was 63.84 years, similar in both sexes. The most frequent reaction detected was Parkinsonism (92), followed by other movement disorders excluding tremor (35), headache (26), tremor (24) and memory disturbances (16). Milder side effects were not recorded. Twenty-seven patients suffered from two different reactions. The chief complaint was related to the adverse reaction in 101 (47.34%) patients. The offending drug was aggravating a previous disease in 32.55%. The usage of the drug was clearly justified in 62.26%, but it seemed unjustified in 30.19%. The offending drug could be withdrawn in 68.40% but in 23.11% this was not possible. Following drug withdrawal, improvement was fast in 26.42% and another 9.91% became asymp-

tomatic more slowly. At follow-up 19.81% still presented the same intensity of symptoms. The high prevalence of, and the importance of adverse reactions in producing several different neurological disturbances, often as a result of treatment which was unjustified, is therefore highlighted.

DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMOUR: A NEWLY RECOGNISED NEOPLASM WITH DISTINCTIVE NEUROIMAGING AND PATHOLOGICAL FEATURES

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Dysembryoplastic neuroepithelial tumour (DNT) is a newly recognised brain mass lesion. Eighteen patients with pathologically proven DNTs were reviewed; only one patient did not have epilepsy. Age at seizure onset ranged from one week to 30 years (mean, nine years). At a median follow-up of 13 months ($n = 15$), 13 patients were seizure-free and two had a more than 80% reduction in seizure frequency. EEG showed localised slow activity in 14/15, and interictal spiking in 12/15 cases.

The temporal lobe was involved in all except one patient, where it involved the cingulate gyrus. MRI features included ($n = 16$): a predominantly intracortical location (16/16), circumscribed hypointensity on T1-weighted images (12/16), hyperintensity on T2-weighted images (15/16), cyst formation (6/16) and grey-white matter blurring (6/16). The tumour was just anterior to, or involved, medial temporal structures in 11 patients.

The cytological composition was heterogeneous, a complex mixture of astrocytes, oligodendroglial-like cells, neurons and germinal matrix. Other pathological features included: calcification (13/18) and dysplastic features (11/18), including duplication of the dentate gyrus in one case. The presence of areas of hypercellularity or marked cellular pleomorphism (11/18), or both, occasional mitoses (11/18), and expression of the proliferating cell nuclear antigen (6/16) support a neoplastic rather than a hamartomatous origin of DNTs.

The detection in vivo of DNTs is important for presurgical planning and prognostication.

NEUROLOGICAL COMPLICATIONS DUE TO CYCLOSPORIN IN KIDNEY TRANSPLANTS

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Neurological complications are reported in 10–25% of patients treated with cyclosporin. These include tremors, seizures, dysaesthesias, neuropathy, and rarer cases of confusion, coma, ataxia, quadriplegia, cerebral blindness, and leukoencephalopathy.

A total of 190 patients with transplanted kidneys operated on at the authors transplant unit since July 1985 were reviewed: 133 were male (70%) and 57 were female (30%) with a mean age of 43.16 (SD 12.17) years (range:14–66). Eleven patients had tremor (5.78%), seven had seizures

(3.68%). There were dysaesthesias in three (1.57%), neuropathy in four (2.1%) and confusion in two (1.05%). Five of them had two complications simultaneously. The mean time before complications began was 98 days after transplant (range:11–370). There were no significant differences between sex, age, the moment complications began, and the number of seizures related to cyclosporin levels, although blood cyclosporin levels three times above normal have been found in neuropathy. The mean number of seizures was 1.85 (range:1–4). It is suggested that they are not treated.

In general, the treatment of neurological complications caused by cyclosporin consists of decreasing the drug dose. It is concluded that it is important to recognise the various types of drug complications and distinguish them from other causes.

STROKE PATTERNS IN YOUNG PATIENTS WITH RIGHT-TO-LEFT SHUNTS DETECTED BY TRANSCRANIAL DOPPLER ULTRASOUND

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Patent foramen ovale has been suggested as a potential reason for paradoxical embolism in patients with cryptogenic stroke. Recently transcranial Doppler ultrasound with contrast infusion has proved more sensitive than contrast transthoracic echocardiography in disclosing right to left shunts (RLS). Using ultrasound, the frequency of RLS and its clinical profile was studied in 29 patients under 45 years who had been included previously in a standard protocol (CT, cerebral angiography, two-dimensional echocardiography and complete laboratory studies) after suffering an ischaemic stroke. RLS was demonstrated in eight patients (27%), five of them showing massive microbubbles in the middle cerebral artery. Patients with cryptogenic stroke had a significantly higher prevalence of RLS (seven of 13, 54%) than patients with an identifiable cause of stroke (one of 16, 16%) ($p = 0.01$). The stroke pattern of the group with RLS showed a trend to a sudden onset of symptoms, with a duration less than 24 hours, cortical infarct on CT scan and a better functional capacity on discharge. Our findings suggest that RLS is a risk factor for stroke in young people and the clinical pattern supports an embolic mechanism.

DETECTION OF ASYMPTOMATIC CIRCULATING CEREBRAL EMBOLI IN PATIENTS WITH POTENTIAL EMBOLIC SOURCES

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The authors have previously demonstrated in a sheep model that thrombus, platelet, and atheroma emboli can be detected in the cerebral circulation using transcranial Doppler ultrasound. We used this technique to study 40 patients with potential cerebral embolic sources, and 10 age-matched normal controls. Recordings of 20 minutes were made from each middle cerebral artery, on to digital audiotape, and analysed by a blinded observer.

Interobserver reproducibility was high; in a subgroup of 10 recordings there was 100% agreement over whether embolic signals were present or absent.

No embolic signals were detected in 10 controls. In six of 15 subjects with recent transient ischaemic attacks or stroke, and carotid stenosis, recording from the ipsilateral middle cerebral artery demonstrated asymptomatic embolic signals with a median frequency of two per 20 minutes. In one of 15 subjects, embolic signals were detected in the middle cerebral artery on the contralateral asymptomatic side; this subject had a 60% asymptomatic carotid stenosis. Twenty-five subjects with prosthetic heart valves were also studied; in one case adequate Doppler signals could not be obtained. In nine of the remaining 24 patients asymptomatic embolic signals were found. They were significantly ($p < 0.01$) more frequent in patients with metallic prosthesis (8/12) than in patients with pig xenografts (1/12). This is consistent with the increased frequency of embolic stroke noted in patients with metallic prostheses.

This new technique may aid in the localisation of the relevant embolic source in patients with stroke, if recording is performed at different sites. If these emboli, like transient ischaemic attacks, are markers for subsequent stroke, it may allow patients at risk to be identified for prophylactic anticoagulation treatment or carotid endarterectomy.

THE MOLECULAR PATHOLOGY OF MOTOR NEURON DISEASE WITH DEMENTIA

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Dementia, often of frontal lobe type is sometimes associated with motor neurone disease (MND). Brain and spinal cord tissue from 33 patients with MND was studied, including 11 cases with dementia. In all cases with MND, typical ubiquitin-immunoreactive inclusions were present in brain stem and spinal cord motor neurons. In 10 of the 11 cases with MND-dementia, ubiquitin-immunoreactive inclusions were present in hippocampal dentate granule cells, and in small neurons of the superficial layers of the frontotemporal neocortex. The inclusions were not identified by antibodies directed against hyperphosphorylated tau, neurofilaments or other cytoskeletal proteins, and were ultrastructurally distinct from Pick bodies. Hippocampal inclusions were present in some MND patients who were not demented. The findings indicate that MND-dementia has a distinctive molecular pathology, and that involvement of limbic cortex is sometimes present in non-demented MND patients.

LATERALITY DIFFERENCES IN THE MEMORY FOR, AND AWARENESS OF, HEMIPLEGIA DURING CAROTID AMYTAL TESTING

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The particular association between anosognosia for hemiplegia and right hemisphere

pathology remains unconfirmed because patients with equivalent left hemisphere pathology may be too asphasic to examine satisfactorily. The intracarotid amytal test gives an opportunity to elucidate the matter by examining memory for hemiplegia soon after recovery from the weakness and any aphasia/confusion.

Thirty-one patients with unilateral temporal lobe pathology (11 right, 20 left), were examined using the test before epilepsy surgery. The median age was 23 (range 12–45) years; six patients had atypical language dominance; 25 had hippocampal sclerosis. The two sides were injected (standard dose 200 mg) on different days, the non-pathological side first. Memory for limb weakness was examined by questioning at the end of the test when recognition of items (objects, etc.) presented during the hemiplegia was also examined. Awareness of arm weakness during the hemiplegia was examined if possible.

More were amnesic for left (27) than for right (12) hemiplegia ($p < 0.001$). Amnesia for left hemiplegia was independent of the side of the pathology.

Amnesia for right hemiplegia was significantly associated with right temporal lobe pathology ($p < 0.01$) (9/11 with right pathology, 3/20 with left), and with impaired memory item recognition ($p < 0.05$).

Anosognosia was recorded during 13 instances of left hemiplegia but only once with right hemiplegia.

The data strongly support hemispheric differences underlying memory/awareness of hemiplegia and anosognosia. They also suggest an additional usefulness for intracarotid amytal in confirming right temporal lobe pathology.

NOTIFICATION RATES IN DRIVERS WITH EPILEPSY

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Members of the Association collaborated in a survey of people holding a driver's licence with a recent history of seizures who were counselled about the effects of these on their driving. Patients received the usual clinician's verbal counselling and written information emphasising the legal requirement to inform the Driver Vehicle and Licensing Authority (DVLA). Patients were asked to return a notification slip with any letter to the DVLA. A central office received details of patients counselled as well as slips returned to the DVLA. Individual patients could not be identified other than by a survey number common to both the recording of clinical details and the DVLA notification slip.

A total of 661 patients were counselled and 173 (26.2%) returned slips to the DVLA. A number of factors increased the likelihood of reporting. These included being prescribed antiepileptic drugs, having driven within the last year, having had a recent accident, being counselled by a consultant rather than a registrar, and increasing age. Interestingly, both overall accident rates and rates for accidents causing injury for this population were not significantly different from recent TRRL surveys in non-epileptic populations. The results have

implications for current regulations on notification following epileptic seizures.

INTRAVESICAL CAPSAICIN FOR TREATMENT OF DETRUSOR HYPERREFLEXIA

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An intravesical instillation of 100 ml of 1 or 2 mmol/l capsaicin has been used to treat detrusor hyperreflexia giving rise to intractable urinary incontinence in 12 patients with spinal cord disease and two other patients with detrusor overactivity of nonspinal origin. Nine patients, all of whom had spinal cord disease, showed some improvement in bladder function. The benefit was only shortlived and partial in four, but the remaining five achieved complete continence while performing intermittent self catheterisation. Urodynamic studies in these nine patients showed an increase in mean bladder capacity from 106 (SD 57) to 302 (SD 212) ml and a fall in the maximum detrusor pressure from 54 (SD 20) to 36 (SD 10) cm of water. There were no short term ill effects from the instillation and the improvement in bladder function lasted for between three weeks and six months when, in some patients, it was repeated.

The improvement in bladder behaviour can be interpreted as showing that capsaicin sensitive afferents play an important role in the pathogenesis of detrusor hyperreflexia in patients with spinal disease. Intravesical capsaicin seems a promising means of treating intractable detrusor hyperreflexia and studies using this substance may shed new light on other disorders of detrusor overactivity that cause incontinence.

NEUROLOGICAL INVOLVEMENT IN ASYMPTOMATIC PATIENTS WITH BEHÇET'S DISEASE

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The involvement of the central and peripheral nervous systems in neurologically asymptomatic patients with Behçet's disease was prospectively investigated. Identification of asymptomatic neurological involvement could be of importance for prognostication and early treatment in the disease. It is believed that there have been no prior reports about evoked potentials, nerve conduction studies, EEG, and MRI in neurologically asymptomatic patients.

Seventeen consecutive, neurologically asymptomatic patients with Behçet's disease were studied. Clinical history and neurological examination was performed by the same neurologist. Studies of evoked potentials, EEG, nerve conduction studies, and MRI (1.5 T) were undertaken in these patients. Physical examination and EEG was normal in all patients. SEPs were abnormal in two of 14 (14.3%), VEPs in five of 14 (35.7%) and BAEPs in five of 14 (35.7%). Nerve conduction studies showed abnormalities in two of 13 (15.3%). MRI was abnormal in five of 13 patients (38.44%). The common pattern was small lesions in the white matter that gave a high MRI signal intensity. It is concluded that asymptomatic neurological involvement in patients with Behçet's disease is quite fre-

quent (76.4%). Abnormalities are most frequently encountered in BAEPs and MRI studies. VEP alterations are not specific and are not necessarily related to CNS involvement. Peripheral nervous system involvement is infrequent and a causal relationship with Behçet's disease is doubtful.

RABIES: AN EXPLANATION FOR THE VAMPIRE LEGEND

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Vampires were cadavers who went out at night and, in the shape of a man or an animal (wolf, dog, bat), attacked people and animals causing their death. Vampires rejected garlic, roses and mirrors; they were hypersexual; their bite converted their victims into vampires, and their corpses were well preserved and full of liquid blood.

The belief in vampires developed early in the 18th century in the Balkan countries, where some epidemics of vampirism occurred. The search for its cause in cemeteries provoked both the intervention of authorities and an extensive debate in Europe. Nowadays, the vampire paradigm is Dracula, a fictional version of the legendary phenomenon.

Vampirism evokes an epidemic zoonoses which involves the limbic system and is transmitted through a bite. The only disease fulfilling these requirements is rabies. The features of furious rabies fit very well with the vampires accounts. Moreover, a rabies outbreak affected the Balkan region around 1725.

Anthropologists defend the existence of real facts behind popular legends. Diseases such as schizophrenia or porphyria have been considered as possible bases for vampirism. The rabies theory (already proposed in 1733!) seems to be the most plausible explanation for the development of the vampire legend.

AN EXPERIMENTAL APPROACH TO ANTIGEN-SPECIFIC IMMUNOTHERAPY IN MYASTHENIA GRAVIS

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In autoimmune diseases, selective immunotherapy should avoid the side effects of generalized immunosuppression. In myasthenia gravis, antibodies directed against the acetylcholine receptor (AChR) are believed to be CD4⁺ T helper (T_H) cell dependent. Therefore, inactivating disease-specific T_H cells should selectively interrupt anti-AChR antibody production. T cell activation requires recognition by its receptor (TcR) of specific antigen (epitope) presented within the cleft of the restricting major histocompatibility complex (MHC) molecule, concurrent with a second, non-specific "costimulatory" signal. To attempt antigen-specific T cell inactivation, a human CD4⁺ T lymphocyte clone (PM-A1), raised from a 15 year old patient's thymus was used. For PM-A1, both the restricting MHC class II element (DR4) and peptide epitope (a144–156) are known. A soluble MHC class II:peptide complex ("Cx"; DR4: p144–163) that would provide the TcR-specific signal, in the absence of co-stimula-

tory signals was used. Cx-preincubation of PM-A1 cells resulted in death (by apoptosis) in up to 50% of cells, and long-lasting highly specific functional inactivation (tolerance) of remaining cells. The effects were time and dose dependent. In tolerant cells previously treated with Cx, fluorescent activated cell sorter analysis of remaining viable cells showed continued down-regulation of IL-2 receptors. Antigen-specific approaches such as this would, in theory, be applicable *in vivo* in myasthenia gravis.

ANTI-ENDOTHELIAL CELL ANTIBODIES IN PATIENTS WITH MULTIPLE SCLEROSIS

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The incidence of anti-endothelial cell antibodies (AECAs) in a population of patients with multiple sclerosis was determined. There is evidence that AECAs may injure vascular endothelia, in particular, the blood-brain barrier. AECAs have been reported previously in serum samples from guinea pigs with acute and chronic relapsing experimental allergic encephalitis, as well as in samples from patients with multiple sclerosis.

Serum samples from 50 patients with multiple sclerosis, 50 patients with systemic lupus erythematosus and 36 healthy controls were examined for AECAs by enzyme linked immunosorbent assays (ELISAs) using cultured endothelial cells from human umbilical cord veins.

IgM antibodies to endothelial cells, but not IgG antibodies, were detected in seven of 50 patients with multiple sclerosis (14%). No correlations were found between AECAs and different clinical or laboratory parameters, including the patients' ages, the course of the disease, and the presence of an exacerbation. There was, however, a significant relationship between a higher score in the extended Kurtzke disability status scale and the presence of AECAs.

These preliminary results show a low incidence of AECAs in patients with multiple sclerosis. The antibody seems to be associated with the more disabled patients. Determining AECAs using cultured brain endothelial cells, however, can be more sensitive.

THE IMMUNOGENETIC BASIS OF MULTIPLE SCLEROSIS

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Twin studies have clearly demonstrated the importance of genetic factors in susceptibility to multiple sclerosis and the immune system is implicated in the pathogenesis. A number of marker systems are now available for the major immune response genes (including T cell receptor β , T cell receptor α and immunoglobulin genes). Several candidate gene loci were studied in a large population of affected sibling pairs, and intrafamily and population-based association studies were performed. The role of the class 2 HLA allele DRw15 is confirmed as a risk factor for disease susceptibility. In addition, evidence is provided of linkage to other genes encoding influential immune response genes, namely the immunoglobulin

heavy chain variable region and T cell receptor β -chain variable region. Linkage to the T cell receptor α locus was not demonstrated and the recently claimed linkage to the 5' end of the myelin basic protein gene is refuted. In conclusion, several regions have been identified which encode genes contributing to susceptibility in multiple sclerosis; and these may act interactively or independently.

SERUM GANGLIOSIDE ANTIBODIES IN MULTIPLE SCLEROSIS

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Multiple sclerosis is an autoimmune disorder, but a unique antigen has not been found. Antibodies against gangliosides (AGA) were studied in patients with multiple sclerosis, and relationships were investigated between ganglioside antibody and subtypes of disease differentiated by their clinical course into relapsing remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS) disease.

Forty-two patients (27 women, mean age 33.6 (SD 10.2)) who fulfilled the criteria of clinically definite multiple sclerosis (25 RRMS, nine SPMS, eight PPMS), 89 patients with systemic lupus erythematosus and 36 healthy controls, were studied. A modification of previously described enzyme linked immunosorbent assay (ELISA) techniques was used to estimate serum IgM and IgG antibodies to gangliosides GM1, AGM1 and GD1a. A total of 47.6% of the patients had high levels of AGA. Anti-GM1 was found in 38% of patients with multiple sclerosis, anti-AGM1 in 23.8% and anti-GD1a in 33.3%. IgG was the isotype most commonly found. All the patients with PPMS ($p < 0.0001$), 33% of those with SPMS and 36% of those with RRMS had AGA. No correlation between AGA, MRI findings, evoked potentials, sex, age of onset, and initial symptoms was found. A correlation between AGA and EEDS was observed ($p = 0.009$).

It is concluded that the presence of AGA is high in patients with multiple sclerosis. In contrast with results reported by other authors, a strong correlation between AGA and PPMS is shown in this study.

MAGNETISATION TRANSFER RATE IMAGING IN MULTIPLE SCLEROSIS

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The discrepancy of magnetic resonance lesion load and disability in patients with multiple sclerosis is unexplained. Magnetisation transfer rate (MTR) images have been suggested to be an indicator of the complexity of macromolecular structure and therefore might offer greater pathological specificity than standard contrast MRI.

Forty-three patients with clinically definite multiple sclerosis and four asymptomatic patients with the radiological diagnosis of small vessel disease were examined. Dual echo brain images were obtained (SE 1500/32/80/5 mm/2.5 mm gap) before and after application of a 64 ms sync pulse 2 kHz off water resonance. The total lesion

area was identified on proton density weighted images and the average MTR was calculated from MTR images.

Patients with clinically severe multiple sclerosis (primary progressive, secondary progressive) frequently showed areas of low MTR ($<10\%$) which were not seen in small vessel disease and only seen to a lesser extent in benign multiple sclerosis. The MTR was lower in all groups with multiple sclerosis than in those with small vessel disease. The MTR in patients with multiple sclerosis with mild disability (EDSS < 3.0) was significantly different from patients with moderate to severe disability (EDSS > 5.0).

MTR images appear to be more specific with respect to the underlying pathology than long repetition time images and correlate with disability in multiple sclerosis. A substantial loss of MTR appears to indicate demyelination or axonal loss, or both.

FATIGUE AND PHYSICAL DISABILITY IN MULTIPLE SCLEROSIS

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Fatigue is a frequent complaint in patients with multiple sclerosis. Its pathogenesis is unknown. The existence of a typical specific fatigue syndrome is disputed. The aim of this work was to determine the link between fatigue and physical and psychological involvement in the disease.

Fifty patients diagnosed with clinically definite multiple sclerosis, category 1a, Poser's criteria, were studied. They were examined using the Kurtzke scale and Hamilton scale for depression and anxiety. An original scale to evaluate severity and qualities of fatigue was used. Fatigue, fatigability and worsening of symptoms with exercise were considered. Characteristics and severity of fatigue were related to involvement in functional systems, depression and anxiety, using nonparametric distribution techniques (Spearman's rank correlation, Kruskal-Wallis analysis of variance).

Thirty-nine patients (78%) reported fatigue; 21 of them signalled this symptom spontaneously. Fatigue was the main symptom in three patients. Fatigue was proportional to pyramidal tract involvement ($r = 0.44$ $p < 0.001$) and mental score ($r = 0.41$, $p < 0.038$). Depression and anxiety were not related to fatigue ($p > 0.05$). Patients in the progressive phase had higher fatigue scores than patients in remission. Disease duration was not proportional to fatigue.

The results suggest a high frequency of fatigue in multiple sclerosis patients. Its severity is proportional to pyramidal and mental involvement.

DEMONSTRATION OF THALAMIC ACTIVATION DURING ABSENCE SEIZURES USING $H_2^{18}O$ POSITRON EMISSION TOMOGRAPHY

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Depth EEG recordings in animal models of absence seizures have demonstrated that generalised spike-wave discharges originate in the thalamus and then oscillate within thalamocortical circuits. If the thalamus is

involved in the generation of generalised spike-wave activity in man, an increase in blood flow at this site would be expected at the time of absence seizures.

Nine patients with idiopathic generalised epilepsy were studied. The patients were hyper-ventilated to induce absences and received an intravenous injection of $H_2^{15}O$ followed by a 90 s high resolution positron emission tomography scan. This was repeated up to 12 times in each subject. EEG was recorded throughout. Scans in which absences occurred were compared with scans in which no absences were recorded. Global differences in blood flow were calculated and any additional significant ($p < 0.05$) focal changes were mapped on a pixel by pixel basis.

A mean 15% increase in global cerebral blood flow was seen in association with absence seizures. In addition, after correction for global effects, there were significant focal increases in blood flow in thalamus.

This study provides evidence for involvement of the thalamus in the pathogenesis of absence seizures in humans.

DETECTION OF HIPPOCAMPAL PATHOLOGY BY T2 RELAXOMETRY

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Hippocampal sclerosis is associated with characteristic MRI abnormalities, including atrophy and T2-weighted signal change. Visual assessment of T2-weighted hippocampal signal is subjective and insensitive, but T2 relaxation may be quantified by relaxometry *in vivo*, aiding the identification of the disease. The influence of time, seizures, and antecedent medical events on hippocampal T2 relaxation time (HCT2) was studied, and the reproducibility and stability of this measure was determined.

Sixty-three patients with chronic epilepsy (55 partial and eight idiopathic generalised) were studied. Relaxation time did not correlate with seizure frequency, duration of epilepsy, or age, but was significantly more abnormal in those patients with a history of a prolonged (over 30 minutes) early childhood convulsion than in those without. In 23 patients, repeated measurement after 115–331 days demonstrated no evidence of systematic change of relaxation time with time. Patients with idiopathic generalised epilepsy had normal times. In four patients, a recent (under 45 minutes) complex partial or secondarily generalised seizure did not alter relaxation times acutely.

Hippocampal relaxation time is a precise, reliable, stable, non-invasive measure of pathology. These results do not suggest progression of hippocampal sclerosis over periods of up to 18 months in these patients.

SUBTHALAMOTOMY IMPROVES MPTP-INDUCED PARKINSONISM IN MONKEYS

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Hyperactivity of the subthalamic nucleus (STN) is a major characteristic of Parkinsonism secondary to substantia nigra lesion. Interruption of the STN-internal pallidum (GPi) pathway is a new stereotaxic

target in Parkinson's disease. The anti-Parkinsonian efficacy of an STN lesion in MPTP-treated monkeys was studied. Four rhesus monkeys had Parkinsonian symptoms induced by MPTP (i.v. 0.15 ± 1 mg/kg) administration over three months. Unilateral subthalamotomy (kainic acid) was performed by standard stereotaxic methods. Severity was rated from zero (normal) to V and by fine manual motor tests. Three monkeys (severity state III/IV) showed marked improvement in spontaneous activity, facial expression, and manual dexterity bilaterally, although significantly greater in the contralateral limb to the lesion. Mild hemichorea was present in two and hemiballismus in one. Levodopa (50 mg twice a day) enhanced the hemidyskinesias moderately. The therapeutic effect has persisted for over eight months after surgery. One monkey (severity stage V) showed chorea in the lower limb contralateral to the lesion but no improvement, and died a few days later.

Subthalamotomy improves Parkinsonism in moderately severe Parkinsonian monkeys, but dyskinesia may be a persistent complication.

NEW STUDIES OF MITOCHONDRIAL DNA REARRANGEMENTS

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The link between rearrangements of mitochondrial DNA and the phenotypes of Kearns Sayre syndrome and chronic progressive external ophthalmoplegia was clearly established in 1988. The major form of mitochondrial DNA rearrangement appears to be a deletion, that is, loss of a segment of the genome, although rare cases of tandem duplication (the presence of an additional sequence) have also been described. The mechanism(s) whereby these rearrangements occur is unknown, although illegitimate recombination and slippage during replication have both been put forward as possible explanations.

Patients with apparent deletions of mitochondrial DNA were reinvestigated and it was discovered that, contrary to previous findings, DNA duplication occurs in most cases examined. The levels of duplicated mitochondrial DNA are very variable but appear highest in patients with Kearns Sayre syndrome. The balance between deleted/duplicated and wild-type DNA varies considerably in patients with both ophthalmoplegia and Kearns Sayre syndrome but the levels of deleted copy appeared to correlate with disease severity. The finding that duplicated mitochondrial DNA is present uniformly in patients with these diseases has important implications for our understanding of the mechanisms involved in generating rearrangements and for our understanding of the pathogenesis of these disorders.

LEBER'S HEREDITARY OPTIC NEUROPATHY: AN INCREASINGLY VARIED CLINICAL SPECTRUM

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Mitochondrial DNA analysis now allows a number of undiagnosed or misdiagnosed

optic neuropathies to be recognised as Leber's hereditary optic neuropathy (LHON) and the clinical spectrum of that disease is correspondingly undergoing reappraisal.

The records of 31 patients (28 male, 3 female) with visual loss due to LHON have been reviewed. Twenty-five had mitochondrial mutations diagnostic of LHON, among which the initial diagnoses included optic neuritis, tobacco-alcohol amblyopia, ischaemic optic neuropathy, optic nerve compression, and post-traumatic chiasmal arachnoiditis. The remainder were diagnosed on clinical features and family history. Age at onset of symptoms averaged 30 years, exceeding 40 years in 27% of cases. A family history was present in 54% of index cases. Neurological disease, including multiple sclerosis, was present in six patients. Visual loss developed over an average of seven weeks (1–36) with an average of 12 weeks delay (0–50) between the development of symptoms in both eyes. Worst visual acuity was always 6/60 or worse, being CF or worse in 71% of eyes. Final visual acuity was better than CF in 45% of eyes and 6/24 or better in both eyes of three patients.

Mitochondrial DNA analysis should be considered in any patient with an optic neuropathy of uncertain aetiology to determine whether LHON is the cause.

ALTERATIONS IN SUPPRESSOR-INDUCER T CELLS IN MULTIPLE SCLEROSIS AND OTHER NEUROLOGICAL DISEASES

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Multiple sclerosis (MS) is a disease in which immune alterations may be involved in its pathogenesis. Some studies have shown that patients exhibit a decrease in suppressor-inducer ($CD4^+CD45RA^+$) T cells during active disease. In order to assess whether this decrease is specific to MS we studied 41 patients with active MS (mean age 30 (SD 9)), and patients with other inflammatory CNS diseases (ID: 28 patients; mean age 38 (SD 14)) and non-inflammatory CNS diseases (NID: 37 patients; mean age 46 (SD 17)) and 50 healthy individuals (mean age 38 (SD 14)). "Case control" comparisons matching for sex and age (SD 5 years) were performed. T lymphocyte subsets $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+CD45RA^+$, $CD4^+CD29^+$, and $CD4^+CD25^+$ were analysed from whole blood by direct immunofluorescence and flow cytometry. All patients were free of immunosuppressants before sampling.

In comparison with matched healthy subjects, the $CD4^+CD45RA^+$ subset showed decreased percentages in MS ($n = 41$; 18.7 (SD 8.4) v 22.8 (SD 7.3); $p = 0.02$) as well as in CNS diseases of both inflammatory ($n = 23$; 19.7 (SD 4.5) v 24.1 (SD 4.8); $p = 0.031$) and non-inflammatory ($n = 31$; 15.5 (SD 8.0) v 20.0 (SD 7.2); $p = 0.029$) origin. No significant changes in cytotoxic/suppressor ($CD8^+$), helper-inducer ($CD4^+CD29^+$), and activated helper ($CD4^+CD25^+$) T cells were detected in MS, ID nor NID groups. On the other hand, higher values of $CD8^+$ T cells were observed in MS than ID ($n = 20$; 32.2 (SD 6.9) v 26.8 (SD 7.1); $p = 0.014$) and NID ($n = 22$; 33.6

(SD 6.1) v 29.7 (SD 7.0); $p = 0.044$) groups. No differences were found between ID and NID groups.

Although the alterations of lymphocyte subsets in MS may still be related to a deficit in functional immune suppression, the decrease of CD4⁺CD45RA⁺ T cells in neurological diseases may be influenced by an alteration in the regulation of the immune system by CNS, caused by the cerebral affection.

CATARACT INCIDENCE IN MYOTONIC DYSTROPHY

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The cataract incidence in an extensive sample of patients with myotonic dystrophy was determined, and the relationship to age of onset and duration of illness. The incidence of cataracts in these patients showed a great variability mainly because of the characteristics of the analysed sample. The present data based on an epidemiological survey could establish tighter quantitation of this clinical feature.

Of the 183 patients registered in Guipúzcoa on August 31, 1991, 76.5% were evaluated and classified, according to slit-lamp examination, into incipient, moderate and severe/or operated groups. Of those examined, 87.1% had cataracts. A total of 83.1% of the patients with no or mild lens opacities, had symptoms of myotonic dystrophy before they were 30 years old, whereas patients with severe lens opacities had initial symptoms of disease in a similar proportion before and over the age of 30 years. Whereas 7.4% of patients aged 30 years or younger presented typical, mature, myotonic cataracts, only 2.5% older than 40 years demonstrated a normal slit-lamp examination. Normal ophthalmological examination rates decreased from 20%, 12%, 11.4% to 0% according to the duration of the illness for one, two, three or more decades respectively.

It is concluded that cataracts were one of the most prominent features of muscular dystrophy with a different age of onset pattern than myotonia. When muscular dystrophy started after the patient was 50 years old or illness duration exceeded three decades or both, cataracts were a universal feature.

THE CEREBELLAR EVOKED POTENTIAL IN MAN

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The short-latency somatosensory potential evoked by median nerve stimulation at the wrist was recorded in 11 normal subjects. A bilateral negative wave was found at 14 ms, and is termed the N14. Its amplitude was greatest over the posterior fossa, where, with bipolar leads, it measured 1.3 (SE 0.1) μ V bilaterally. It was significantly smaller contralaterally when a tripolar derivation of the posterior fossa leads was made ($p = 0.02$).

Eight patients with unilateral cerebellar lesions and one patient with predominantly unilateral cerebellar damage were also investigated. The N14 recorded with bipolar leads over the lesion (1.0 (SE 0.1) μ V)

was significantly smaller than either the contralateral N14 (1.5 (SE 0.2) μ V, $p = 0.002$), or the N14 recorded in normal subjects ($p = 0.035$). Similarly, the N14 recorded with a tripolar derivation of the posterior fossa leads was smaller over the lesion (0.6 (SE 0.2) μ V) than over the contralateral cerebellar hemisphere (1.3 (SE 0.2) μ V, $p < 0.002$).

It is concluded that the N14 recorded over the posterior fossa is generated in the cerebellum. This is the first recording of the cerebellar evoked potential with scalp electrodes in humans. The recording technique is simple and may have clinical applications.

USE OF THE ROCKING BED IN THE TREATMENT OF NEUROGENIC RESPIRATORY INSUFFICIENCY

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A range of techniques for domiciliary ventilation is necessary in the management of respiratory insufficiency due to neuromuscular disease. The choice of support is determined by several factors including severity of respiratory impairment, extent and distribution of weakness, and overall prognosis.

Fifty-three patients who have received ventilatory support with a rocking bed are described. Diagnoses included previous poliomyelitis (30 patients), muscular dystrophy (12), motor neuron disease (four), acid maltase deficiency (four) and a miscellaneous group (three). Patients were treated because of respiratory insufficiency characterised by diaphragm weakness (46), progressive nocturnal hypoventilation (49), with or without respiratory failure (32). The bed was used by 43 patients for a mean of 16.0 years (range 1 month to 35 years), most patients requiring between 6 and 11 hours nocturnal ventilation. The bed was generally well tolerated and associated with symptomatic relief and amelioration of arterial blood gas abnormalities. It was discontinued in 17 patients because of patient discomfort (nine) and increasing respiratory insufficiency (eight).

The rocking bed is a noninvasive form of ventilatory support, which can be used in hospital or at home. It is a valuable adjunct in the treatment of respiratory insufficiency associated with diaphragm paralysis, bulbar weakness, and skeletal deformities, and in the management of terminal dyspnoea.

VIDEO GAME ASSOCIATED SEIZURES: HETEROGENEOUS PHENOMENA

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Video game associated seizures have recently been the subject of considerable public and media concern. First described in 1981, 20 further cases have appeared in the English published reports. These were analysed along with seven of the authors' own cases and four described by DeMarco.

These seizures have been considered to be photosensitive, analogous to television induced seizures, although video games involve other known provocative factors. Of

the 31 patients, only 20 had electroclinical evidence of idiopathic generalised epilepsy: typical absences, absence status, and myoclonic jerks were described, sometimes preceding generalised tonic-clonic seizures that were reported predominantly. At least four patients had juvenile myoclonic epilepsy and one juvenile absence epilepsy. Only 16/31 had photoconvulsive responses to intermittent photic stimulation. Nonphotic precipitating factors included sleep deprivation, early morning fatigue, emotional arousal, mental concentration, and seizure self-induction for pleasure.

Phenomena suggesting partial onset (usually visual auras) with secondary generalisation were described in nine patients. Sudden changes in background illumination or sensitivity to more complex visual stimuli may be important precipitating factors in these patients. EEG evidence of occipital lobe sensitivity was found in five patients.

VGS is not a homogeneous entity, and should not always be equated with photosensitive epilepsy.

MAGNETIC RESONANCE IMAGING OF THE OPTIC NERVE IN BENIGN INTRACRANIAL HYPERTENSION

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Benign intracranial hypertension is a condition of obscure aetiology characterised by increased intracranial pressure, acute or chronic papilloedema, and normal CSF constituents in the absence of an intracranial mass. MRI was used to investigate the width of the optic nerve sheath, which might reflect pressure changes.

Ten normal controls, 13 patients with benign intracranial hypertension and one patient with increased intracranial pressure caused by a mass lesion were examined. Mildly T2 weighted 3 mm coronal fast spin echo images (TR3400/TE69ef) were obtained with an in-plane resolution of 0.4 mm in 10 minutes imaging time.

The width of the optic nerve sheath was symmetrical in normal controls but varied between individuals. It narrows progressively towards the orbital apex with no CSF signal seen in the optic canal. In patients, the ring of CSF surrounding the optic nerve was demonstrated up to the optic canal (on 6-7 slices) which contrasted with normal controls (4-5 slices). The asymmetry of papilloedema correlated with the width of the optic nerve sheath.

Increased size of the subarachnoid space correlates with raised intracranial pressure provided the optic nerves themselves are of normal size. MRI is potentially useful in monitoring treatment.

ANTIBODIES TO GANGLIOSIDE LM1 IN GUILLAIN-BARRÉ SYNDROME

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Previous studies of antibodies to gangliosides in Guillain-Barré syndrome (GBS) have concentrated on ganglioside GM1 which is the most abundant ganglioside in the brain and only a minor component of peripheral nerves. The most abundant ganglioside in peripheral nerve myelin is ganglioside LM1. Ganglioside LM1 was

purified from human erythrocytes and its purity confirmed by thin layer chromatography and immuno-overlay with a human IgM monoclonal antibody known to be reactive with ganglioside LM1. An enzyme linked immunosorbent assay (ELISA) was used to look for antibodies to ganglioside LM1 in the serum samples from 28 patients with GBS, 25 with chronic idiopathic demyelinating polyradiculoneuropathy (CIDP), 28 with other neuropathies (ON), and 28 normal control (NC) subjects. Serum samples were tested at a dilution of 1/200 and regarded as positive, which gave an optical density reading of more than 2 SD above the NC mean. IgM antibodies were identified in eight GBS, three CIDP, three ON and one NC serum samples. IgG antibodies were identified in three GBS, one CIDP, one ON and one NC serum samples. IgA antibodies were not identified in any sera. Sera with high optical density readings in this assay were shown to bind to ganglioside LM1 in human cauda equina by immuno-overlay. Patients with GBS with IgM and IgG antibodies in their serum had a similar age and sex distribution and clinical course to those without. Only 5/28 patients with GBS had antibodies to ganglioside GM1 and these were not closely associated with antibodies to ganglioside LM1. It is concluded that antibodies to ganglioside LM1 are found in the serum samples of patients with GBS more often than in those of normal subjects or those with other neuropathies. Such antibodies are more common than antibodies to ganglioside GM1 and may be important in the pathogenesis of some cases.

TUNISIAN DUCHENNE-LIKE AUTOSOMAL RECESSIVE MUSCULAR DYSTROPHY: FROM THE CLINICAL DESCRIPTION TO GENE MAPPING

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Various studies on myopathies in Tunisia showed the presence of a particular and frequent form of an autosomal recessive muscular dystrophy, similar to Duchenne muscular dystrophy but affecting boys and girls. The age of onset varied from three to 12 years. Muscle weakness progressively involved pelvic, then scapular muscles. It was associated with hypertrophy of the calf muscles. The evolution was variable from one patient to another, even between siblings, but usually the course was comparable with that of Duchenne muscular dystrophy. Creatine kinase levels were very high, particularly in early stages of the disease. The muscle biopsy showed a dystrophic feature with necrosis, regeneration, and increase of the connective tissue. Dystrophine was normal in quantity and quality. This muscular dystrophy was mapped to the long arm of chromosome 13.

RISK ESTIMATES FOR FIRST DEGREE RELATIVES OF PATIENTS WITH APPARENT SPORADIC MOTOR NEURON DISEASE
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Patients with motor neuron disease resident in the three counties of south east Wales

(population 1 394 000) from 1 November 91 to 31 December 92 were ascertained through general practitioners and the neurology department records: 62 out of 71 (51 men, 20 women) index cases agreed to be visited. These individuals were clinically reviewed, had a detailed family history taken and, after discussion, had a blood sample taken for testing for the X-linked bulbospinal muscular atrophy mutation. The period prevalence was 5.0/100 000 with a mean age of onset of 59.4 (SD 12.9) years. One 66 year old man was found to have the mutation. A single, definite, first degree relative pair was identified, of whom only one was included in the data. The index cases had a total of 131 offspring and 173 siblings. The risk estimates, by current age, for these first degree relatives of patients with apparently sporadic motor neuron disease decreased from one in 85 at age 20 years to one in 1683 at age 80 years. These estimates clearly require confirmation in an independent sample, based, as they are, on a single "event".

UPPER AIRWAY DYSFUNCTION IN PATIENTS WITH PARKINSON'S DISEASE

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To investigate the prevalence of upper airway obstruction in Parkinson's disease, maximal inspiratory and expiratory flow-volume curves were obtained in 63 patients with different stages of disease not selected for respiratory symptoms. Parkinson's disease was evaluated by the unified Parkinson's disease rating scale, the Webster's scale, and Hoehn and Yahr staging. Patients with higher scores in the scales had lower CVF%, PIF, and PEF%. Those with fluctuations or dyskinesias or both, had lower CVF% and FEV%. Several significant correlations existed between the scales and spirometric parameters, but they were of very low range. Thirty-one patients (49.2%) had pathological flow-volume curves (21 type A, nine type B, and one obstructive). The clinical profile and the duration of the disease did not influence the pattern of the curve. Physiological evidence without clinical symptoms of upper airway obstruction was observed in three cases. A spirometric restrictive ventilatory defect (FEV₁/CVF \geq 80%) was observed in 54 patients (85%), whereas only one patient had generalized airway obstruction.

Abnormal flow-volume loop contour is a usual finding in Parkinson's disease. This probably reflects involvement of the upper airway musculature, that in some patients can produce clinical obstruction. Generalized airflow limitation seems not to be an important feature of Parkinson's disease.

RISK FACTORS FOR PARKINSON'S DISEASE: A CASE-CONTROL STUDY IN THE PROVINCE OF CACERES, SPAIN

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A case-control study was performed in a mixed rural and urban province, involving 74 patients with Parkinson's disease and

148 unselected age and sex-matched controls, attempting to look for possible risk factors for the disease. Rural living, well-water drinking, a positive family history, and postural tremor, were associated with an increased risk of Parkinson's disease, with results regarding exposure to pesticides near to statistical significance. Alcohol-drinking habits in men were associated with a decreased risk of disease, and data on cigarette smoking in men neared statistical significance. There was no link between the risk of Parkinson's disease and the following variables: exposure to industrial toxins; agricultural work; cranial trauma; previous common illnesses including some infections, arterial hypertension, diabetes mellitus, coronary heart disease, and thyroid disease; and coffee and tea drinking habits.

T CELL RECEPTOR V, USAGE IN GUILLAIN-BARRÉ SYNDROME

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It has been shown previously that T cells bearing activation markers are present in increased numbers in the blood of patients with Guillain-Barré syndrome (GBS). The authors studied whether the T cell receptor (TCR) V β gene usage by the activated and nonactivated T cells of patients with GBS and normal controls is restricted. The mononuclear cells were separated from the heparinised blood of four patients with acute GBS and four normal controls. Activated T cells were then separated from the nonactivated ones, using a monoclonal antibody to the IL-2 receptor CD25 and the Immunicon magnetic separation system, followed by cytofluorographic analysis. Single strand cDNA was synthesised from total RNA. The amount of TCR C β cDNA in each sample was measured semiquantitatively by titrating the cDNA TCR C β chain by polymerase chain reaction (PCR). A linear PCR was carried out to determine levels of V β 1 to V β 20 in cDNA. PCR products were electrophoresed on 1.5% agarose gels, blotted, and hybridised with a ³²P-labelled adenosine triphosphate C β probe. Southern blots of the PCR products were autoradiographed and scanned. There was marked heterogeneity of the TCR V β usage by all the samples. There was predominant usage of one V β chain gene, V β 15, by the activated T cell pools from all of the four patients with GBS, but not by any of the other samples. This preliminary result suggests that the TCR V β chain gene usage by circulating activated T cells in GBS may be relatively biased towards V β 15. This might be due to a predominant T cell response against a restricted epitope.

ABNORMALITIES OF COGNITIVE FUNCTION AND CEREBRAL ACTIVATION IN AMYOTROPHIC LATERAL SCLEROSIS

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Positron emission tomography and neuropsychological testing were used to compare cortical function in nondemented patients with amyotrophic lateral sclerosis (ALS) and normal, age matched controls.

Regional cerebral blood flow was measured at rest and while subjects performed paced, stereotyped or freely-selected movements of a joystick with their right hand.

Regional cerebral blood flow at rest was significantly ($p < 0.01$) reduced in patients with ALS in the primary sensorimotor, premotor, and motor association cortices. During upper limb movement, patients showed significantly ($p < 0.001$) greater activation than controls in the face area of the contralateral sensorimotor cortex. Neuropsychological assessment revealed significantly ($p < 0.05$) impaired verbal fluency and picture recall. During freely selected joystick movements, a subgroup of patients with impaired verbal fluency showed significantly ($p < 0.01$) impaired activation of the right parahippocampal gyrus, anterior thalamic nuclear complex, and anterior cingulate cortex in comparison with patients with normal fluency.

Reduced regional cerebral blood flow at rest and altered somatotopy during limb movement in the sensorimotor cortex of patients with ALS probably reflects loss of pyramidal neurons. The correlation between abnormalities of cognitive function and impaired activation of a limbo-thalamo-prefrontal circuit in patients with ALS suggests that neuronal vulnerability in the disease may extend beyond the cortical motor system.

INTERGENERATIONAL VARIATIONS OF THE CTG SEQUENCE RELATED TO MYOTONIC DYSTROPHY: A CLOSE BUT NOT UNIVERSAL RELATIONSHIP BETWEEN ANTICIPATION AND AMPLIFICATION

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The intergenerational variation of the CTG sequence related to myotonic dystrophy was studied with regard to parental sex and its possible relationship with the anticipation phenomenon. Parent-child pairs were ascertained from an extensive epidemiological survey conducted in Guipúzcoa, Spain. All possible pairs including asymptomatic carriers were included if 50% or more sibship members were screened. cDNA25 and polymerase chain reaction techniques were used to assess the CTG amplification. Clinical anticipation, if found, was tabulated in decades. A total of 78.9% of the 71 pairs analysed (41 had the father as the affected parent, and 30, the mother) showed CTG amplification. Contraction was observed in 14.1% of the pairs. Ten of the 14 pairs, where the child was clinically asymptomatic, had an affected father (60% of these father-asymptomatic pairs showed an intergenerational contraction). The same father was implicated in five of these pairs. In the mother-child pairs, only four sibs were considered to be asymptomatic (in these cases, DNA amplification was mild or zero, but contraction was absent). Clinical anticipation coexisted in four pairs with intergenerational DNA contraction.

Although clinical anticipation seems to be related to DNA amplification, it may be possible with DNA contraction. Tendency towards contraction appears clearly associated with a transmission through the male germline and could contribute to perpetuate

the genetic reservoir of muscular dystrophy in the population.

PRIMARY LEPTOMENINGEAL SARCOMATOSIS: A DIFFICULT DIAGNOSIS

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Primary leptomeningeal sarcomatosis is a rare neoplastic disorder presenting different clinical patterns. A 24 year-old woman is reported who first had a polyneuropathy, then a spinal cord compression with sphincter disturbance, cranial nerve involvement with bilateral facial paresis, and deafness. Finally, the hypothalamus was involved, producing amenorrhea, diabetes insipidus, and later, panhypopituitarism. Routine radiological, haematological, and biochemical blood and urine analysis, including screening for sarcoidosis, porphyria, lysosomal disorders, CNS bacterial, or fungal infections failed to reveal abnormalities. CSF examinations showed an increasing hyperalbuminorrachia ranging from 372 mg/100 ml to 1535 mg/100 ml without pleocytosis. Cranial CT revealed an obstructive hydrocephalus requiring a derivative shunt. Cranial and spinal MRI did not show the tumour. The general condition of the patient continued to deteriorate because of scar infections and she died 48 months after the first symptoms. The postmortem examination showed a spinal cord diffusely infiltrated by a tissue that reached the subarachnoid space, involving the cranial nerves, lumbar roots, basal vessels, and chiasm. Serial sectioning of the parenchyma revealed nodular masses in the brain stem and hypothalamus. Microscopically, the infiltration was described as a primary leptomeningeal sarcomatosis. Meningeal biopsy, usually the best diagnostic procedure, could not be performed in this patient. The authors agree with previous reports about the difficulty of antemortem diagnosis.

COLOUR DOPPLER ASSESSMENT OF THE BASAL CEREBRAL ARTERIES BEFORE CAROTID ENDARTERECTOMY

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Transcranial colour coded sonography (TCCS) is a recent development in non-invasive cerebral vascular imaging. Unlike conventional transcranial Doppler techniques, the intracranial arteries are imaged using colour flow ultrasound allowing correction for the angle of insonation and more accurate determination of blood flow velocities.

TCCS was used to study the cerebral circulation in 24 patients before carotid endarterectomy. The anterior (ACA), middle (MCA) and posterior cerebral arteries (PCA) were imaged via the transtemporal window using 2.25 MHz colour flow ultrasound. Blood flow velocities were determined using 2 MHz pulsed wave Doppler. Five patients had discrete arterial segments showing high velocity, turbulent blood flow with low velocity, damped Doppler waveforms distally, compatible with intracranial stenotic disease. Bilateral MCA mainstem

stenoses and unilateral MCA mainstem stenoses were detected in two patients each and stenoses of the ACA and PCA in one patient. In six patients, high velocity, retrograde blood flow in the ACA ipsilateral to the carotid stenosis was detected indicating collateral flow via the anterior communicating artery.

TCCS can detect collateral flow in the circle of Willis and intracranial stenotic disease. In conjunction with extracranial carotid ultrasound, the extra- and intracranial cerebral circulation can now be imaged rapidly and noninvasively.

SULPHUR METABOLISM IN GIANT AXONAL NEUROPATHY

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Giant axonal neuropathy is an autosomal recessive childhood disorder in which a peripheral neuropathy is associated with features of central nervous system involvement and characteristic dense and frizzy scalp hair. Peripheral nerve biopsy reveals distal axonal swellings filled with intermediate filament collections. The underlying metabolic abnormality is unknown, but disordered sulphhydryl metabolism is suspected. Three affected children in two families were studied. Abnormal fasting plasma levels of cysteine and sulphate were found. Fasting levels of cysteine were significantly low in two affected sibs (0.192, 0.2019 nm/mg protein, 95% CI 0.38-0.68) in one family when compared with age matched controls, whereas sulphate levels were significantly low in a separate family with one affected child (0.309 nm/mg protein, 95% CI 7.1-13.9). Furthermore, affected children in each family demonstrated markedly abnormal metabolism of the probe drug carbocysteine. These results incriminate the enzyme cysteine B liase in the pathogenesis of the disease.

THE ROLE OF MICROEMBOLI IN THE NEUROPSYCHOLOGICAL SEQUELAE OF CORONARY ARTERY BYPASS SURGERY

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Neuropsychological tests, sensitive to quite subtle changes in intellectual function, have detected impaired cerebral function in a third of patients after coronary artery bypass surgery.

A total of 105 patients were randomised to two groups, one of which had an extra-arterial line 40 µm screen filter. One hundred (50 in each group) completed the protocol with transcranial Doppler monitoring of microemboli in the middle cerebral artery, and serial neuropsychological testing (10 test battery) before and at eight days and eight weeks post surgery.

At eight weeks, four of 49 cases who were filtered showed more than 1 SD drop in performance in two or more tests compared with 12 of 45 without filtration ($p < 0.03$). When the microembolic count was less than 200, 8.6% exhibited such a deficit: with

counts over 1000, 43% had a deficit. The greatest difficulties were with the Rey Auditory learning test. On each of its seven limbs, the patients who had not been filtered performed less well. The difference in the second limb, for example, was significant at $p < 0.007$ (Mann-Whitney U test).

The results argue strongly for an aetiological role for microemboli in the neuropsychological deficit and have obvious implications for practical management. This clinical situation is offered as a model for the assessment of neuroprotective drugs in development.

MULTIPLE SCLEROSIS IN SIBLING PAIRS

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As part of continuing genetic linkage study, 232 sibling pairs concordant for multiple sclerosis were recruited by a system of national advertisement, of which 127 families were visited in order to obtain clinical data on year and age of disease onset, initial symptoms, disease course and severity, and additional family history. Subsequent analysis resulted in 26 exclusions and intrafamilial comparisons are reported on the remaining 101 families.

Intrafamilial clustering was observed for age but not year of onset, further supporting a genetic contribution to disease aetiology. No similarities were seen in severity or initial symptom; however, the overall familial recurrence rate was 36%, six times that recorded in a recently reported local prevalence study.

These results suggest that clinical features of familial disease may, in part, be due to inherited factors, and that risk of developing the disease is not spread uniformly among families. This has important implications in the management and counselling of individuals with familial disease.

COMPARISONS OF BRAIN AND CEREBROSPINAL FLUID VOLUME IN PATIENTS WITH BENIGN INTRACRANIAL HYPERTENSION AND NORMAL CONTROLS

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It is unclear whether raised intracranial pressure in benign intracranial hypertension (BIH) results from an increased volume of blood, brain or CSF. In order to determine the relative changes in volume of the cerebrum and cranial CSF in BIH, CT brain scans of 30 cases were compared with those of 30 age and sex matched normal controls. In a further seven cases, cranial CSF volumes were measured before and after treatment or remission of disease, using a quantitative MRI technique, and compared with controls. All cases had papilloedema, CSF pressure over 25 cm of water and normal CSF constituents. Matched case-control CT scans were independently assessed by two neuroradiologists, blind to the diagnosis. The lateral ventricles were graded as small, normal, or large; the third ventricle as normal, slit, or absent; and the sulci and basal cisterns as normal or effaced. For each case-control pair, an assessment was made as to which scan showed the smaller ventri-

cles and cisterns. The table shows the assessments on which both neuroradiologists agreed.

Quantitative indices of ventricular size measured on the 60 CT scans, suggested significantly smaller ventricles in patients with BIH than controls (all $p < 0.01$): mean (SD) third ventricular diameter = 0.7 (0.46) v 1.44 (0.68) mm; Huckman index = 49 (21) v 73 (27); inverse cella media index = 0.074 (0.021) v 0.124 (0.06).

MRI scanning revealed lower mean (SD) CSF volumes in cases than controls: ventricular CSF = 7.4 (3.2) ml v 15.2 (6.5) ml, $p < 0.05$; sulcal CSF = 81 (33) ml v 93 (39) ml, $p = \text{NS}$. Following treatment or remission, CSF volume increased in patients with BIH: ventricular CSF = 10.4 (4.2) ml, $p = 0.1$; sulcal CSF = 96.8 (14.8) ml, $p = 0.08$. These results indicate that cerebral volume is increased and cranial CSF volume is decreased in BIH, and do not support the much quoted hypothesis that BIH is due solely to an increased resistance to CSF drainage.

	Small lateral ventricles	Slit/absent 3rd ventricle	Effaced sulci \pm cisterns	Smaller ventricles and cisterns
Case	9	15	13	24
Control	1	2	1	4

PERIPHERAL NEUROPATHY IN HIV INFECTION, SMALL AND LARGE FIBRE INVOLVEMENT, CLINICAL AND NEUROPHYSIOLOGICAL STUDY

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The aim of this study was to determine the extent of small fibre involvement in HIV infected patients in various CDC classes. Eighty-one homosexual men were included, 21 seronegative controls, 36 asymptomatic HIV seropositive (CDC class II/III) and 23 with AIDS (CDC class IV). A neurological examination, nerve conduction studies and thermal threshold tests for cooling and warming were carried out.

Peripheral neuropathy was present clinically in six out of 20 seropositive men (21%) and 10 out of 36 asymptomatic HIV seropositive men (28%) and 11 out of 24 symptomatic CDC class IV patients (46%). The warm test threshold means were 1.58, 1.68, and 3.38 in the three groups ($p = 0.01$ (analysis of variance $F_c = 3.12$, $F = 4.84$); the mean threshold in the warm test in the three groups with clinical neuropathy was abnormal (3.83, 2.3, and 4.06) with no significant difference between the three groups ($p = 0.33$ (analysis of variance $F_c = 3.4$, $F = 1.15$). The mean warming threshold in the three groups without clinical neuropathy was significantly different (0.61, 1.44, and 2.81; $p = 0.008$ (analysis of variance $F_c = 3.1$, $F = 5.2$). The cold test mean threshold was abnormal in the three groups with clinical peripheral neuropathy, but not in those without.

The results show that small fibres are almost always involved if peripheral neuropathy is present and that small fibres can be affected in HIV infection with or without AIDS in the absence of a large fibre neuropathy.

PRIMARY EMPTY SELLAE ASSOCIATED WITH SYRINGOMYELIA

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The association between chronic hydrocephalus and syringomyelia is known. Much more infrequent is the association of benign intracranial hypertension and primary empty sellae. Syringomyelia and primary empty sellae in the same patient is an association that has rarely been reported.

Between February 1987 and February 1993, 46 patients with cervical syringomyelia, confirmed by MRI studies, were admitted to the authors' service. This report assesses the association between syringomyelic cavity and primary empty sellae to compare possible changes after treatment and to clarify the significance of this association. Three patients with syringomyelia and primary empty sellae are reported, all of them with a Chiari malformation. Syringomyelic symptoms and signs were the reason for medical consultation in two cases and both had surgical treatment (ventriculoperitoneal shunt in case 1, who presented with concomitant hydrocephalus, and decompression of posterior fossa in case 2). Both patients improved after surgery and the size of the sella (arachnoidocele) was reduced. Endocrinological symptoms were the reason for medical consultation in case 3, in whom the syringomyelic cavity, demonstrated by MRI, was clinically asymptomatic.

In conclusion, the findings reinforce the hypothesis that hydrodynamic disturbances of the CSF created by the Chiari malformation, with raised intraspinal and intracranial pressure transmitted by pulsation of the CSF, would be responsible for both the syringomyelia and the primary empty sella. Recognition of the empty sellae would be possible only after MRI and only in the few cases where a congenital defect in the diaphragma sellae exist.

INFARCTION OF THE SPINAL CORD. A CLINICAL AND MRI FOLLOW UP STUDY OF EIGHT CASES

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Spinal cord infarction (SCI) occurs infrequently and has many causes. The diagnosis of SCI, and particularly of an anterior spinal artery syndrome (ASAS), can now be confirmed by MRI, whereas, in the past, only necropsy confirmation was possible. Pathophysiology and long term prognosis may become better known and treatment become more consistent.

The longitudinal study and clinical features of eight patients suffering from SCI is reported. They were examined by the authors and studied with MRI, often sequentially. Three groups are considered: one includes four cases of ASAS at cervical level, the second includes two cases of ASAS at thoracic level and the third group has infarction of the conus medullaris, one of them developed during surgical repair of an infrarenal aortic aneurysm. Motor and sensory sequelae are assessed in each case, as well as the possible aetiological factors.

In conclusion, recovery after ASAS tends

to depend on the severity of the initial deficit. At the cervical level, clinical, morphological, and electrophysiological findings argue in favour of a selective occlusion of the C7 right radiculomedullary artery as being responsible for the ASAS. At thoracic level, the artery preferentially occluded seems to be the sulcocommissural artery as a consequence of disc compression. Finally, an underlying anomaly of the pattern of arterial supply is a likely predisposing factor for conus medullaris infarction. Generally, the long term prognosis of SCI is not necessarily unfavourable.

PRIMARY PROGRESSIVE APHASIA: A COMPARISON OF CT, MRI AND CEREBRAL PERFUSION SPECT IMAGING
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Primary progressive aphasia can be defined as a progressive failure of language for two or more years, with preservation of activities of daily living. In such patients, neuropsychological testing confirms sparing of general and nonverbal cognitive function. Whereas the clinical features of this syndrome have been well documented, the accompanying neuroradiological findings have not.

Thirteen patients with primary progressive aphasia were studied. Ten underwent cranial CT, 12 had MRI and 12 had cerebral perfusion studies using ^{99m}Tc -HMPAO SPECT. CT and MRI images were reviewed qualitatively by two independent assessors. Initial qualitative assessment of SPECT images was confirmed by quantitative analysis. CT was relatively insensitive at detecting abnormalities, images being within normal limits for age in six patients. Focal abnormalities were seen in 10 out of 12 patients on MRI, and in all 12 patients who underwent SPECT. The most frequent finding was unilateral temporal atrophy/perfusion defect. MRI allowed localisation of atrophy primarily to the superior and middle temporal gyri. In two patients, MRI was normal, but significant temporal lobe perfusion deficits were revealed by SPECT.

MRI and SPECT are therefore the imaging modalities of choice in primary progressive aphasia and are complementary, revealing abnormalities of structure and function respectively.

EXERCISE ENHANCES POSTURAL HYPOTENSION IN PRIMARY AUTONOMIC FAILURE, BUT NOT IN IDIOPATHIC PARKINSON'S DISEASE
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Factors such as food ingestion can worsen postural hypotension in autonomic failure. The effects of exercise are unknown. Two groups with primary autonomic failure were therefore studied: pure autonomic failure (PAF, $n = 15$) and Shy-Drager syndrome (SDS, $n = 15$). Patients with idiopathic Parkinson's disease without autonomic dysfunction (IPD, $n = 5$) and normal subjects ($n = 10$) were also studied.

All were studied after an overnight fast. Postural blood pressure changes were recorded before, and 10 minutes after, nine minutes of incremental supine exercise on a

bicycle ergometer. During exercise, mean (SD) supine blood pressure fell in PAF (149(5)/89 (3) to 124(4)/70 (3) mmHg, each $p = 0.0001$) and SDS (151(7)/95 (3) to 138(5)/83 (3), NS and $p < 0.01$), but increased in controls (123 (4)/77 (3) to 159 (4)/96 (3), each $p < 0.001$) and IPD (133 (6)/83 (2) to 157 (5)/92 (2), each $p = 0.01$). Blood pressure fell to lower levels on standing, following exercise, in PAF (pre 98 (5)/61 (5), post 78 (3)/49 (3) mmHg, each $p < 0.05$) and SDS (pre 105 (4)/74 (5), post 84 (6)/60 (5), each $p < 0.05$). In IPD there was no significant difference (pre 121 (4)/83 (3), post 119 (1)/83 (3). In the controls, blood pressure was unchanged.

It is concluded that exercise accentuates postural hypotension, even after 10 minutes rest, in both PAF and SDS. This may be caused by persisting, uncompensated skeletal muscle vasodilatation. Exercise does not lower blood pressure in normal subjects or in IPD.

A COMPARISON BETWEEN FAST SPIN ECHO AND CONVENTIONAL SPIN ECHO IN THE DETECTION OF MULTIPLE SCLEROSIS
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The characteristic brain lesions of multiple sclerosis (MS) are readily detected by MRI employing conventional T_2 and proton density weighted spin echo (SE) pulse sequences. Obtaining T_2 -weighted SE images of the whole brain is, however, time consuming. Fast spin echo (FSE) permits the generation of T_2 -weighted images with contrast very similar to that obtained with conventional SE in a fraction of the time (typically three minutes *v* 10 minutes). Their relative sensitivity in detecting MS lesions, however, is unknown. Brain MRI was therefore carried out in six patients with clinically definite MS using both dual echo (short and long echo time) SE and FSE. Each of the four resulting sets of images was first viewed in isolation and the sets then compared. There was no significant difference in the number of lesions detected by SE and FSE (404 and 398 respectively). SE demonstrated more periventricular lesions than FSE (147 *v* 133), FSE more in the posterior fossa (80 *v* 60). For both sequences the short echo time images showed more lesions than the long echo time.

It is concluded that FSE should supplant SE as the preferred sequence in MS. In patients undergoing repeated imaging, especially in the context of treatment trials, this would result in considerable saving in time, and hence costs, as well as improved patient compliance.

A PILOT STUDY OF INTRA-ARTERIAL THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE
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Thrombolytic therapy for the early treatment of patients with acute ischaemic stroke is promising. A pilot study of intra-arterial streptokinase was undertaken in patients presenting with acute stroke, thought to be caused by major intracranial artery occlusion, in whom CT had excluded intracerebral haemorrhage.

The trial treatment, streptokinase 250 000 IU or placebo (normal saline 50 ml) was given intra-arterially proximal to the cerebral arterial occlusion which was documented angiographically.

Only four patients entered the trial in 10 months. Two others had angiography but one subsequently declined to participate and another had an asymptomatic aneurysm. Angiography prolonged the time to treatment by at least one hour and was very labour intensive. Recanalisation at 24 hours after treatment was complete in two patients treated with streptokinase; slight in one, who had received the placebo; and there was persistent occlusion in the fourth patient, who had received streptokinase.

The trial stopped because of slow recruitment, and the testing of intra-arterial thrombolysis seems too impractical for future evaluation. It is unclear whether thrombolysis is an effective or safe treatment for acute ischaemic stroke. Intravenous streptokinase is a far more practical treatment and is currently being evaluated in the UK as part of the Multicentre Acute Stroke Trial-Italy (MAST-I) study.

MULTIPLE SYSTEM ATROPHY WITH LEWY BODIES: A REVIEW OF 15 CASES
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Two years ago Hughes *et al* reported a case of multiple system atrophy with additional numerous Lewy bodies in the brainstem and cortex, suggesting co-existing Parkinson's disease. The authors have since encountered three similar cases, and the clinical features of these four patients and 11 additional cases from published reports are reviewed.

The median age of onset was 58 (47-75) years and the median survival five (2-11) years. Seven (47%) patients presented with Parkinsonism, five (33%) with autonomic dysfunction, three (20%) with combinations of autonomic dysfunction and Parkinsonism (two) or cerebellar ataxia (one). Tremor at rest was seen in six (40%) patients, but classical, pill-rolling, rest tremor was only documented in one. Six patients received trials of levodopa and half of them showed a good (two) or excellent (one) response. Two patients developed dyskinesias and fluctuations. Cerebellar and pyramidal signs were present in five (33%) and seven (47%) of the patients, respectively. Neuropathological examination revealed marked degeneration of substantia nigra in all cases, and of striatum in 14, and some degree of olivopontocerebellar atrophy in all but one case. It is concluded that, as the clinical spectrum of these 15 cases with mixed pathology is the same as that found in pure multiple system atrophy, the additional presence of Lewy bodies does not modify its clinical expression.

OLFACTORY FUNCTION IN PROGRESSIVE SUPRANUCLEAR PALSY AND CORTICOBASAL DEGENERATION
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Olfactory function is impaired in patients with Parkinson's disease (PD). Apart from

MPTP induced Parkinsonism, Parkinsonism-dementia complex of Guam, progressive supranuclear palsy (PSP) (five cases) and multiple system atrophy (MSA) other specific forms of Parkinsonism have not been studied. Preliminary data on two groups of patients with corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are therefore presented.

To date, University of Pennsylvania smell identification test (UPSIT) scores have been obtained by self administration in nine subjects with PSP and in seven subjects with CBD, age and sex matched with patients with PD and healthy controls.

One way analysis (p value at 0.05) showed no significant difference between patients with PSP and healthy controls. Subjects with CBD, however, scored significantly worse than the healthy controls (27.1 (SD 1.7) v 30.6 (SD 2.8)), but the difference was considerably less than that found in patients with PD. The latter scored significantly worse than healthy controls (19.6 (SD 5.7) v 30.6 (SD 2.8)). In addition, the group with PD also performed significantly

worse than those with CBD (19.6 (SD 5.7) v 27.1 (SD 1.7)) and PSP (16.7 (SD 5.2) v 30.3 (SD 5.1)). It is concluded that olfactory function is strikingly preserved in PSP and mildly affected in CBD. This contrasts with gross deficits found in PD. Olfactory dysfunction may therefore be a useful tool for differentiating akinetic-rigid syndromes.

MODE OF ACTION OF THE NEUROLATHYRISM TOXIN β -OXALYL-AMINO-L-ALANINE

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The neurotoxin β -N-oxalylamino-L-alanine (BOAA), found in *Lathyrus sativus* seeds, is thought to be the causative agent of neuro-lathyrism. The action of BOAA was investigated by focal injection in the rat hippocampus, and the pathological outcome was compared with the effects of injections of α -amino-3-hydroxy-5-methyl-

isoxazole-4-propionate (AMPA), kainate (KA) or N-methyl-D-aspartate (NMDA). Cellular damage in the pyramidal (CA1-CA4) and dentate granule neurons (DG), induced by the excitatory amino acids, was assessed histologically 24 hours after the injection. BOAA (50 nmol) induced hippocampal toxicity with a highly selective pattern of regional cellular damage, affecting particularly the CA1, CA4 and DG subfields. This pattern of cellular damage was similar to that induced by AMPA and NMDA, but not KA. BOAA induced neurotoxicity was prevented in a dose-dependent manner by focal coinjection of the nonNMDA receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(F)quinoxaline (NBQX), but not by MK-801. The free radical scavenger DMSO also protected against damage induced by BOAA (but not by AMPA) in the hippocampus. These results indicate that the toxicity of BOAA is mediated by the AMPA receptor site, and that BOAA may, in addition, impair free radical scavenging mechanisms in the brain.